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ORIGINAL REPORT

Integrating nine prescription opioid analgesics and/or four signal detection systems to summarize statewide prescription drug abuse in the United States in 2007[†]

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SUMMARY

Purpose Integrate statewide rankings of abuse across different drugs and/or signal detection systems to summarize prescription drug abuse in each state in 2007.

Methods Four signal detection systems (Opioid Treatment Programs, Key Informants, Drug Diversion, and Poison Centers) that covered heterogeneous populations collected data on the abuse of nine opioids: hydrocodone, immediate-release oxycodone, tramadol, extended-release [ER] oxycodone, fentanyl, morphine, methadone, hydromorphone, and buprenorphine). We introduce here linearized maps which integrate nine drugs within each system; four systems for each drug; or all drugs and systems.

Results When rankings were integrated across drugs, Rhode Island, New Hampshire, Maine, West Virginia, and Michigan were in the highest tertile of abuse in three systems. When rankings were integrated across signal detection systems, there was a geographic clustering of states with the highest rates for ER oxycodone (in Tennessee, Mississippi, Kentucky, Ohio, Indiana, Michigan, and in Massachusetts, New Hampshire, Maine, and Vermont) and methadone (Massachusetts, Rhode Island, New Hampshire, Maine, Vermont, Connecticut, and New Jersey). When rankings were integrated across both drugs and signal detection systems, states with 3-digit ZIP codes below 269 (i.e., from Massachusetts to West Virginia): Massachusetts, New Hampshire, Maine, Vermont, Washington DC, Virginia, and West Virginia were in the highest tertile and only Delaware was in the lowest tertile.

Conclusions We have presented methods to integrate data on prescription opioid abuse collected by signal detection systems covering different populations. Linearized maps are effective graphical summaries that depict differences in the level of prescription opioid abuse at the state level. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — abuse; maps; non-parametric methods; prescription opioid analgesics; signal detection systems

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INTRODUCTION

As we approach the end of the first decade of the 21st century, prescription opioid abuse remains a primary public health concern, as indicated by several studies which have shown increased rates of abuse.[1–6] Surveillance systems of prescription opioid abuse collect data on the number of cases of abuse or intentional exposure cases, and signal detection methodology is used to find statistically significant increases in abuse. In this report, we used data collected by four different surveillance systems whose primary aim was to identify signals of abuse, and thus hereafter we refer to them as signal detection systems. Each one of the four signal detection systems collects data on the abuse of a particular drug (e.g., hydrocodone) at specific geographic locations (e.g., three-digit ZIP code [3DZ]) in a given unit of calendar time (e.g., a quarter). These data, coupled with an assessment of therapeutic exposure (e.g., the number of

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individuals to whom a drug is prescribed), provide the essential information to calculate rates of abuse, and therefore permit determination of the risk/benefit ratio of a particular drug.[7–9] Specifically, we have used the unique recipients of a dispensed drug (URDD) (Verispan Inc.) as the denominator in the calculation of rates, as they represent a reasonable proxy for the amount of a drug used in the population.[8]

In this report, we used data collected in 2007 by the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System.[7] The RADARS® System utilizes four signal detection systems, each covering heterogeneous populations with respect to their geographical location and recognized proclivity toward prescription drug abuse. In addition, the RADARS® System via the four signal detection systems monitor the abuse cases of 77 specific products, which in this report we combined into nine drug classes. Statewide rates of abuse can be calculated by drug and signal detection system and summarized in a total of 36 maps to illustrate geographical locales with high rates of abuse. However, using 36 maps to summarize prescription drug abuse would be cumbersome, and therefore we have developed and implemented methods to (1) integrate rankings of statewide abuse across nine prescription opioids within each signal detection system resulting in four maps (one for each signal detection system); (2) integrate rankings of statewide abuse across four signal detection systems for a given prescription opioid resulting in nine maps (one for each drug); and (3) integrate rankings of statewide abuse across both nine drugs and four signal detection systems, resulting in one map describing the overall rate of abuse in the United States. Since signal detection systems cover populations with different risks of abuse, and since it is well known that different drugs have differing nationwide rates of abuse,[3,9] it is essential to implement appropriate methods when summarizing statewide abuse integrated over different drugs and different signal detection systems.

In this report, we present a non-parametric approach to summarize prescription opioid abuse in the United States using the rank ordering of the statewide rates of abuse for each of the drugs and for each of the signal detection systems available to the RADARS® System. The methodological challenge is to weight the ranks of the statewide rates to appropriately integrate nine drugs with different risk profiles and/or four signal detection systems that monitor different and complementary populations. Herein, we propose the use of 36 nationwide rates of prescription drug abuse from four signal detection systems and nine drugs as a proper weighting technique to calculate the abuse percentile for each of the 50 states and Washington, DC. The states can be divided into tertiles (highest, middle, lowest) based on their abuse percentiles, which can then be used to produce maps of three colors that properly characterize statewide opioid abuse. By capitalizing on the numerical order of the 3DZ by states, we also provide a graphical procedure ("linearized maps") to simultaneously and succinctly depict several maps in one figure to facilitate the comparison of signal detection systems and/or drugs of interest.

METHODS

Radars® system

The RADARS® System is a post-marketing surveillance system that provides rapid, accurate, timely, and geographically specific data for use in risk management programs.[7] The System utilizes a Scientific Advisory Board of specialists in addiction, law enforcement, drug regulation, post-marketing surveillance, and epidemiology.

In this report, we focused on the nine commonly prescribed opioid drug classes included in the RADARS® System: hydrocodone, immediate-release [IR] oxycodone, tramadol, extended-release [ER] oxycodone, fentanyl, morphine, methadone, hydromorphone, and buprenorphine. To collect nationwide data from heterogeneous populations, the RADARS® System is comprised of four signal detection systems that cover different geographic areas in the United States: Opioid Treatment Programs (OTP), Key Informants, Drug Diversion, and Poison Centers.

OTPs

The methods and characteristics of the OTP signal detection system, as managed and coordinated by the American Association for the Treatment of Opioid Dependence, have been previously described.[10] Briefly, the OTP participating in the study are funded through federal/state public insurance programs and grant mechanisms in addition to being privately funded. These programs are located in large metropolitan cities, rural towns, and suburban areas in more than 30 states in the United States, and utilize both methadone and buprenorphine in treating patients with opioid dependence. Each OTP distributes an anonymous survey to every patient within the first week of voluntary admission into the treatment program. Questions on the survey instrument are designed to collect information related to opioid drug abuse over the previous 30 days.

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Key informants

In 2007, the Key Informants were located in a total of 153 unique 3DZ, representing urban, suburban, and rural locations. This signal detection system, which has been described in earlier studies[3,7–8] is composed of a large group of treatment center directors (i.e., key informants) specializing in the treatment of adult and adolescent drug addiction. In a quarterly survey, the Key Informants provided the number of individuals who: first, using Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)[11] criteria for abuse had a diagnosis of prescription drug abuse and second, abused an opioid analgesic in the previous 30 days.

Drug diversion

Drug Diversion is a signal detection system that includes 300 investigators, from all 50 states and Washington, DC.[7,12] Briefly, this nationwide sample of law enforcement agencies is geographically diverse, whereby its agencies are located in rural, suburban, and urban areas. Most of the participating agencies are municipal police departments and multi-jurisdiction drug task forces. Participating agencies receive a survey every quarter that elicits the total number of *new* cases of diversion reported to and/or investigated by the diversion units during the previous three months.

Poison centers

In 2007, the Poison Centers signal detection system of RADARS® was comprised of 43 (70%) of the 61 United States poison centers. These 43 centers covered a total of 40 states and by the fourth quarter of 2007 served a population of nearly 200 million individuals.[13] Trained nurses, pharmacists, physicians assistants, and physicians at each of the participating poison centers use standard computerized data collection forms and submit data to RADARS® on a weekly basis. Internal validity checks are performed by both the original center and the coordinating center (Rocky Mountain Poison and Drug Center). A further description of the Poison Center data as an indicator for prescription opioid misuse and abuse, as well as special quality control measures implemented by the RADARS® System taken to verify exposure reason and product codes, has been published previously.[9,14–16]

STATISTICAL ANALYSES

Denominator and rates

The therapeutic exposure (denominator) to each of the nine prescription opioids was quantified by the number of URDD in each calendar quarter at each 3DZ by Verispan, LLC (Yardley, Pennsylvania).[8] Summation of the URDD over all 3DZ within a state[17] yielded the URDD at the state level. For each of the four signal detection systems and each of the nine drugs, statewide rates of abuse were calculated for 2007 by dividing the total cases reported at the covered 3DZ in the state by the total URDD at the covered 3DZ in the state. Likewise, the 2007 nationwide rates of abuse were calculated for each signal detection system and for each drug by dividing the total cases over all states by the total URDD over all states.

Methods to integrate statewide rankings of abuse over drugs and/or signal detection systems

A three-color nationwide map for each one of the 36 combinations of 4 signal detection systems and 9 drugs could be obtained by simply grouping the rankings of the statewide abuse rates into 3 tertiles. The key statistical challenge is how to integrate either (1) the rankings of the nine drugs within a signal detection system to produce four maps or (2) the rankings of the four signal detection systems for a given drug to produce nine maps, or (3) both rankings of drugs and signal detection systems to produce one map. The first case of integrating the ranks for the nine drugs within a signal detection system to contrast the putative heterogeneity of abuse to opioids in different states corresponds to the two-way layout of non-parametric methods.[18] Specifically, "blocks" are the nine drugs and "treatments" are the 50 states and Washington, DC.[18] The test statistic to compare states is based on the mean of the ranks received by a given state for each of the nine drugs. However, a state with the highest rank of abuse for a drug with a high overall level of abuse (e.g., methadone) should not be treated the same as a state with the highest rank of abuse for a drug with a low overall level of abuse (e.g., tramadol). In other words, the blocks are not a nuisance.[18] Hence, to incorporate the overall level of abuse of each of the drugs when integrating the ranks, we used the nationwide rates as the basis for weights to arrive at a weighted average of the ranks of the nine drugs for each state. By weighting the statewide rankings this way, a middle rank for a drug that has a high nationwide rate of abuse (e.g., methadone) will have a similar contribution to the weighted average as a high rank for a drug with a moderate nationwide rate of abuse (e.g., morphine).

For the second case (i.e., integrating the ranks for the four signal detection systems for a given drug) we had to further adjust for the heterogeneity in the populations being studied by different signal detection systems. In other words, OTP which serves individuals with opioid dependence has higher overall levels of abuse than the general population served by the Poison Centers. To account for the differences in the overall level of abuse between each of the signal detection systems, instead of simply using the nationwide rates themselves as the basis for the weights, we used the ratio of the nationwide rates relative to the median of the nine nationwide rates for the drugs within a signal detection system. Thus, each state will have a weighted average of up to four ranks (some states are not covered by all four signal detection systems and in these instances the number of ranks in the weighted average will equal the number of signal detection systems covering the state).

When both drugs and signal detection systems were integrated, each state had a weighted average of up to 36 ranks corresponding to the nine drugs and the number of signal detection systems that cover the state.

Additional details on defining the weights and calculating the weighted average of the ranks for each of the three cases of integrating ranks are included in the Appendix.

Each weighted average of signal detection systems and/or drugs for a given state results in a state score which can be interpreted simply as the percentile of abuse that a given state occupies among all 50 states. The percentiles were categorized into tertiles (i.e., if a state was >67th percentile it was placed in the highest tertile, if a state was between the 33rd percentile and the 67th percentile it was placed in the middle tertile, and if a state was less than the 33rd percentile it was placed in the lowest tertile). By assigning different colors to the states in different tertiles, one can produce a three-color map in which the darkest colors represent states in the highest tertile. To visualize a sequence of maps in a single graph (i.e., a map for each of the nine drugs) we devised linearized maps, which capitalize on the geographical ordering of the 3DZ in the United States. Specifically, the states were ordered along the y-axis from bottom to top by the range of 3DZ for the state (Massachusetts: 010–027, Rhode Island: 028–029,. . ., Washington: 980–994, and Alaska: 995–999). This ordering allows for the identification of contiguous geographic areas with high rates of abuse that would be lost if another ordering was used (i.e., alphabetical order).

RESULTS

Therapeutic exposure

In Figure 1, the average URDD per quarter in 2007 is shown in the $\log_{10}$ scale for each of the 50 states and Washington, DC and each of the nine prescription opioid products. The states are listed along the x-axis by the rank ordering of the average URDD per quarter for hydrocodone (i.e., California had the greatest URDD and Washington, DC had the fewest). In nearly every state, hydrocodone had the largest URDD per quarter, ranging from 16 503 in Washington, DC to 1 692 927 in California (median = 226 141 in Colorado; inter-quartile range [IQR]: 74 561–515 871). IR oxycodone had the second largest URDD per quarter in most states (median = 59 789 in Nevada; IQR = 33 782–159 253), followed by tramadol (median = 46 899 in Connecticut; IQR = 13 957–107 938), ER oxycodone (median = 13 480 in Connecticut; IQR = 5007–21 462), fentanyl (median = 10 984 in Minnesota; IQR = 3732–21 599), morphine (median = 11 217 in Colorado; IQR = 4872–20 360), methadone (median = 7105 in Maryland; IQR = 2878–13 497), hydromorphone (median = 3109 in Iowa; IQR = 1361–7651), and buprenorphine (median = 1724 in South Carolina; IQR = 469–3899).

Coverage area of the four signal detection systems

Table 1 presents the number of 3DZ out of a possible 909 3DZ that were covered by each signal detection system in at least one quarter in 2007. The number (percentage) of 3DZ covered in 2007 by the Key Informants, OTP, Drug Diversion, and the Poison Centers were 153 (17%), 246 (27%), 556 (61%), and 707 (78%) 3DZ, respectively.

Table 1 also presents the number (percentage) of states with different coverage levels for each of the four signal detection systems in 2007. The number of states whose 3DZ were all covered by OTP, Key Informants, Drug Diversion, and Poison Centers were 1, 1, 20, and 35, respectively. OTP covered at least 50% of the 3DZ of 12 (24%) of the 50 states and Washington, DC. Similarly, Key Informants, Drug Diversion, and Poison Centers covered at least 50% of the 3DZ of 1 (2%), 37 (73%), and 38 (75%) states, respectively. Drug Diversion was the only system to cover at least one 3DZ in all 50 states and Washington, DC.

Cases of prescription opioid abuse at the nationwide level

Table 2 presents the total number of cases of prescription opioid abuse (or intentional exposure cases for Poison Centers) in 2007 reported by each of the four signal detection systems. The Poison Centers covered more 3DZ ($n = 707$) than the other three signal detection systems, which in part explains that for five

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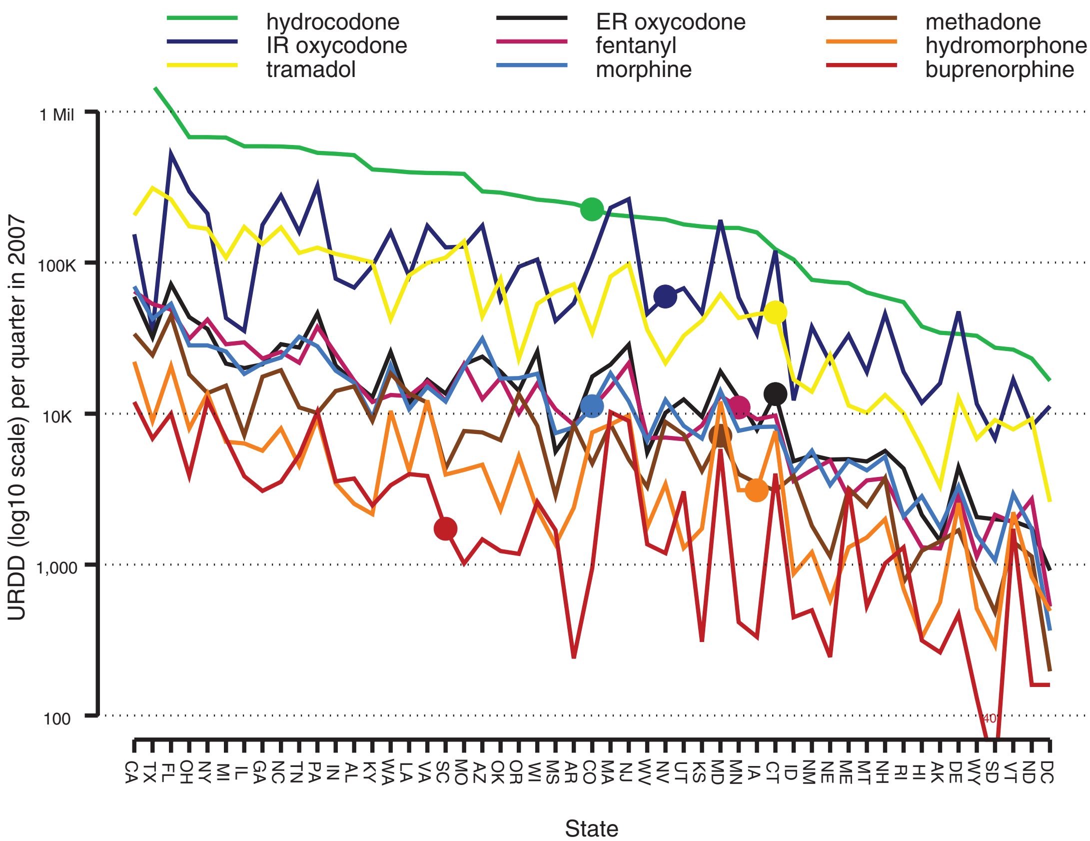

Figure 1. Statewide level exposure to prescription opioids in 2007: average URDD over four quarters of 2007; closed circles indicate states with the median URDD for each prescription opioid. States on the *x*-axis are ordered according to the URDD for the drug of highest use: hydrocodone

of the nine drugs (hydrocodone, IR oxycodone, tramadol, morphine, and methadone), Poison Centers reported the largest number of cases. Within each signal detection system and consistent with it having the greatest therapeutic exposure, hydrocodone had the greatest number of cases reported by Key Informants (6596), Drug Diversion (6005), and Poison Centers (11 931). Similarly, buprenorphine, which had the lowest therapeutic exposure, also had the fewest number of cases for both OTP (208) and Drug Diversion (165), the second fewest for Poison Centers (559), and the third fewest for Key Informants (864). In contrast, in spite of a large therapeutic exposure, tramadol had a relatively small amount of cases reported for OTP (390), Key Informants (569), and Drug Diversion (296).

Nationwide rates of prescription opioid abuse

Table 3 presents the nationwide rates of abuse per 10 000 URDD for each of the four signal detection systems and for each of the nine prescription opioids. For OTP, Key Informants, Drug Diversion, and Poison

Table 1. Coverage area of each signal detection system in 2007

Coverage area	Signal detection system			
	OTP	Key Informants	Drug Diversion	Poison Centers
No. of unique three-digit zip codes	246	153	556	707
No. (%) of states* with				
complete coverage	1 (2%)	1 (2%)	20 (39%)	35 (69%)
75% - <100% coverage	1 (2%)	0 (0%)	6 (12%)	2 (4%)
50% - <75% coverage	10 (20%)	0 (0%)	11 (22%)	1 (2%)
25% - <50% coverage	12 (24%)	14 (27%)	10 (20%)	2 (4%)
>0% - <25% coverage	11 (22%)	31 (61%)	4 (8%)	0 (0%)
no coverage	16 (31%)	5 (10%)	0 (0%)	11 (22%)

*50 states and Washington, DC

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Table 2. Total number of cases for nine prescription opioids in 2007 reported for each of the four signal detection systems

Drug	Signal detection system			
	OTP*	Key Informants†	Drug Diversion	Poison Centers‡
# of three-digit ZIP codes covered	246	153	557	707
Hydrocodone	1927	6596	6005	11 931
IR oxycodone	1565	2389	2694	3957
Tramadol	390	569	296	3545
ER oxycodone	3154	4605	1637	1586
Fentanyl	685	912	322	776
Morphine	937	996	613	1322
Methadone	2341	1938	936	2463
Hydromorphone	451	740	301	401
Buprenorphine	208	864	165	559

*OTP did not cover any three-digit ZIP codes of Arkansas, Delaware, Hawaii, Iowa, Kansas, Minnesota, Montana, North Dakota, Nebraska, New Mexico, Oklahoma, South Dakota, Utah, Wisconsin, Wyoming, Washington, DC in 2007.
†Key informants did not cover any three-digit ZIP codes of Alaska, Arkansas, Hawaii, South Carolina, Vermont in 2007.
‡Poison Centers did not cover any three-digit ZIP codes of Alaska, Arkansas, Delaware, Missouri, Mississippi, North Carolina, New Mexico, Oregon, Utah, Wisconsin, Washington, DC in 2007.

Centers, the drugs with the highest rates of abuse in 2007 were methadone (50.681 cases per 10 000 URDD), ER oxycodone (49.881 cases per 10 000 URDD), methadone (13.594 cases per 10 000 URDD), and methadone (17.747 cases per 10 000 URDD), respectively. The median nationwide rates of abuse of the nine drugs for each signal detection system are indicated in bold (OTP: 10.298 cases per 10 000 URDD from buprenorphine; Key Informants: 13.351 cases per 10 000 URDD from morphine; Drug Diversion: 5.240 cases per 10 000 URDD from morphine; and Poison Centers: 4.953 cases per 10 000 URDD from hydromorphone). Hydrocodone, despite having the greatest therapeutic exposure, consistently had either the lowest or second lowest rate of abuse in each system. Tramadol had the lowest nationwide rate in three of the four systems. For all of the drugs (with the exception of tramadol and methadone), the highest rates came from the Key Informants.

Size of nationwide prescription opioid abuse relative to the sum of the nationwide abuse rates

We present the sizes of each of the nationwide prescription opioid abuse rates for each of the nine drugs within a given signal detection system in parentheses and *below* each of the main entries in Table 3. For example, in OTP, the nationwide rate of

Table 3. Nationwide rates of prescription opioid abuse per 10 000 URDD by drugs and signal detection systems in 2007 with median nationwide rate for each signal detection system highlighted in bold

Drug	Signal detection system			
	OTP	Key Informants	Drug Diversion	Poison Centers
Hydrocodone	1.122 (8.5%) (0.8%)	4.004 (23.3%) (2.0%)	2.239 (33.2%) (4.2%)	2.228 (35.0%) (4.0%)
IR oxycodone	2.655 (15.6%) (1.9%)	4.004 (18.2%) (2.0%)	3.083 (35.6%) (5.8%)	2.503 (30.6%) (4.5%)
Tramadol	1.042 (10.9%) (0.7%)	1.629 (13.1%) (0.8%)	0.474 (9.7%) (0.9%)	3.065 (66.4%) (5.5%)
ER oxycodone	35.325 (32.3%) (25.4%)	49.881 (35.1%) (25.1%)	11.828 (21.2%) (22.4%)	5.977 (11.4%) (10.6%)
Fentanyl	9.278 (29.9%) (6.7%)	12.698 (31.5%) (6.4%)	2.710 (17.1%) (5.1%)	3.212 (21.5%) (5.7%)
Morphine	11.869 (26.9%) (8.5%)	**13.351** (23.3%) (6.7%)	**5.240** (23.3%) (9.9%)	5.640 (26.5%) (10.0%)
Methadone	50.681 (34.5%) (36.4%)	42.535 (22.3%) (21.4%)	13.594 (18.2%) (25.7%)	17.747 (25.1%) (31.6%)
Hydromorphone	17.072 (27.4%) (12.3%)	26.383 (32.7%) (13.3%)	7.386 (23.3%) (14.0%)	**4.953** (16.5%) (8.8%)
Buprenorphine	**10.298** (13.0%) (7.4%)	44.110 (43.0%) (22.2%)	6.300 (15.6%) (11.9%)	10.822 (28.4%) (19.3%)

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methadone abuse of 50.681 cases per 10 000 URDD was 36.4% of the sum of the nationwide abuse rates per 10 000 URDD of all nine prescription opioids (i.e., $0.364 = 50.681/[1.122 + 2.655 + 1.042 + 35.325 + 9.278 + 11.869 + 50.681 + 17.072 + 10.298]$).

Likewise, we present the sizes of each of the nationwide prescription opioid abuse rates for a given signal detection system for each of the nine drugs in parentheses and to the *right* of each of the main entries in Table 3. These were determined by first dividing the nationwide rate of abuse by the median nationwide rate. For example, for hydrocodone these ratios were $1.122/10.298 = 0.109$, $4.004/13.351 = 0.300$, $2.239/5.240 = 0.427$, and $2.228/4.953 = 0.450$ for OTP, Key Informants, Diversion, and Poison Centers, respectively. Next, for a specific drug, the value of each ratio was divided by the sum of the ratios to determine the relative degree of nationwide prescription opioid abuse for each signal detection system. For example, 0.0848 for hydrocodone in OTP was determined by dividing 0.109 by the sum of 0.109, 0.300, 0.427, and 0.450.

Statewide prescription opioid abuse-integrating nine drugs within each signal detection system

We obtained a statewide score for each state, integrating the rankings of statewide abuse of nine drugs within each signal detection system. For example, since West Virginia had the seventh largest rate for hydrocodone in OTP (and OTP covered a total of 35 states in 2007) it was assigned a ranking = 29/35. Additionally, West Virginia had the largest rate for IR oxycodone (ranking = 35/35), the sixth largest rate for tramadol (ranking = 30/35), the largest rate for ER oxycodone (ranking = 35/35), the seventh largest rate for fentanyl (ranking = 29/35), the fifth largest rate for morphine (ranking = 31/35), the seventh largest rate for methadone (ranking = 29/35), the second largest rate for hydromorphone (ranking = 34/35), and the fifth largest rate for buprenorphine (ranking = 31/35). Weighting these rankings by the sizes of the nationwide rates for OTP shown in Table 3, West Virginia had a state score equal to:

$$
\begin{aligned}
&[(29/35) \times 0.008] + [(35/35) \times 0.019] + \\
&[(30/35) \times 0.007] + [(35/35) \times 0.254] + \\
&[(29/35) \times 0.067] + [(31/35) \times 0.085] + \\
&[(29/35) \times 0.364] + [(34/35) \times 0.123] + \\
&[(31/35) \times 0.074] = 0.894
\end{aligned}
$$

which can be interpreted as West Virginia having a high rate of abuse, as it was at the 89.4th percentile of the distribution of the ranks of opioid abuse in the OTP signal detection system.

The states in each of the three tertiles are depicted in Figure 2 for each of the four signal detection systems. States in the highest tertile are indicated by a dark circle, those in the middle tertile by a medium colored circle, and those in the lowest tertile by the lightest colored circle. Open circles depict states not covered by a given signal detection system. Additionally, we have included a color-coded bar graph on the right-hand side of Figure 2 that depicts for each state, the number of signal detection systems that are in each of the three tertiles. Rhode Island, New Hampshire, Maine, West Virginia, and Michigan were in the highest tertile for three of four systems and have bars that are three-fourths dark and one-fourth light or medium color. Conversely, Arizona was in the lowest tertile for three of four systems (bar graph is three-fourths light color), and Texas was the only state in the lowest tertile for all four systems (bar graph is entirely a light color).

Statewide prescription opioid abuse-integrating four signal detection systems for each drug

We obtained a statewide score for each state integrating the rankings of statewide abuse of up to four signal detection systems for each drug. For example, in the case of methadone, Maryland had the 32nd largest rate in OTP (ranking = 4/35), the 18th largest for Key Informants (ranking = 29/46), the 27th largest rate in Drug Diversion (ranking = 24/50), and the 7th largest rate for Poison Centers (ranking = 34/40). After weighting these rankings with the sizes of the nationwide rates for methadone for each of the four signal detection systems, Maryland had a state score equal to:

$$
\begin{aligned}
&[(4/35) \times 0.345] + [(29/46) \times 0.223] + \\
&[(24/50) \times 0.182] + [(34/40) \times 0.251] = 0.481
\end{aligned}
$$

which can be interpreted as Maryland having a moderate rate of methadone abuse, as it was close to the median of the distribution of the ranks of methadone abuse.

The states in each of the three tertiles are depicted in Figure 3 for each of the nine drugs. In contrast to Figure 2, there are no open circles because the combination of the four signal detection systems covers the entire United States. Based on the color coded bar graphs on the right hand side of the figure, West Virginia and Alaska were the only two states in the highest tertile for all nine drugs. Except for

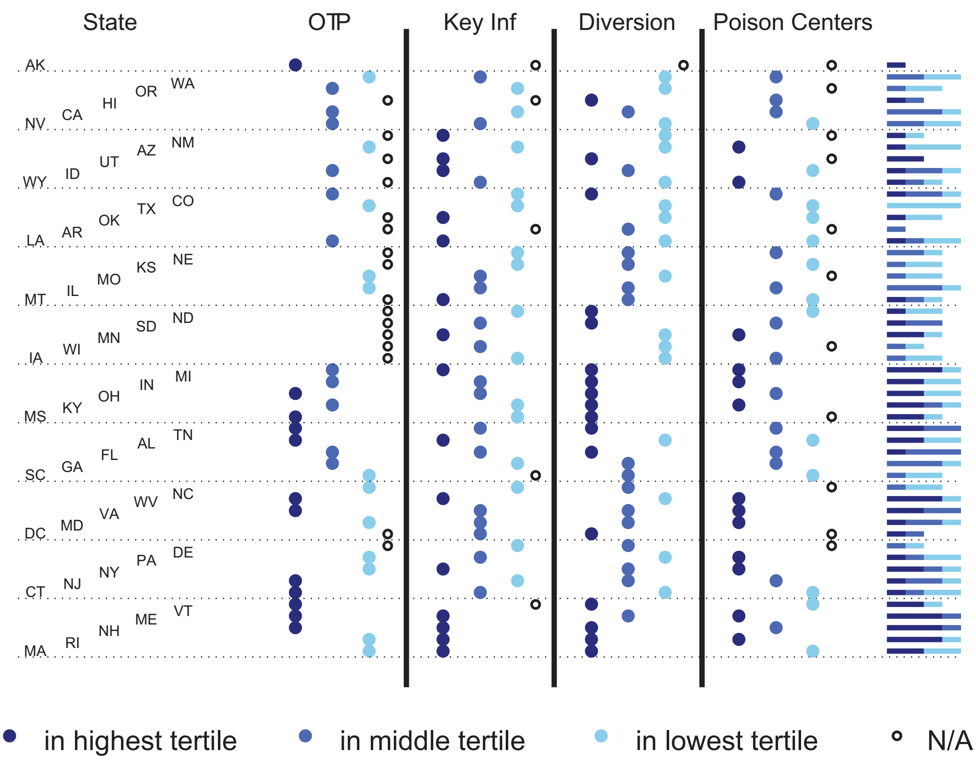

Figure 2. Linearized map of the tertiles of statewide rates of prescription opioid abuse: combining nine prescription opioids (hydrocodone, IR oxycodone, tramadol ER oxycodone, fentanyl, morphine, methadone, hydromorphone, buprenorphine) within each signal detection system; OTP = Opioid Treatment Programs, Key Inf = Key Informants

hydrocodone in Maine, hydromorphone in Michigan, and methadone in Utah, these states were in the highest tertile for all other drugs. Indiana and Minnesota were in the highest tertile for seven of the nine drugs, while Mississippi and South Dakota were in the highest tertile for six of the nine drugs. In contrast, South Carolina, Kansas, and Oregon were in the lowest tertile for all nine drugs; Delaware and Iowa were in the lowest tertile for eight of the nine drugs.

Statewide prescription opioid abuse-integrating both signal detection systems and drugs

We obtained a statewide score for each state integrating the rankings of statewide abuse across all nine drugs and up to four signal detection systems. The states in each of the three tertiles are depicted in Figure 4. For the twenty states with 3DZ above 600 (i.e., from Illinois to Alaska), there were only two states (Idaho and Alaska) in the highest tertile. Among the states in the highest tertile, the five states with the highest rate of abuse were Alaska, Maine, West Virginia, Minnesota, and Michigan. In contrast, for the 14 states with 3DZ below 269 (i.e., from Massachusetts to West Virginia), there was only one state (Delaware) in the lowest tertile. Among the states in the lowest tertile, the five states with the lowest rates of abuse were Texas, Delaware, Oregon, Kansas, and South Carolina.

DISCUSSION

We have presented and implemented methods that can be used to appropriately integrate nationwide rates of prescription opioid abuse across different drugs and/or different signal detection systems to summarize prescription opioid abuse in each of the 50 states and Washington, DC in 2007. Integrating across drugs within a given signal detection system (see Figure 2) provided an overall description of opioid abuse in populations covered by a given system; each state was classified by a percentile that not only combined the statewide rankings of abuse for all nine prescription opioids, but also incorporated the size of the nationwide rate of abuse for each of the nine drugs. Similarly, integrating across signal detection systems for a given prescription opioid (see Figure 3) provided a description of the abuse of a particular drug using data from signal detection systems that cover different geographic locations and populations. Finally, both drugs and signal detection systems were integrated (see

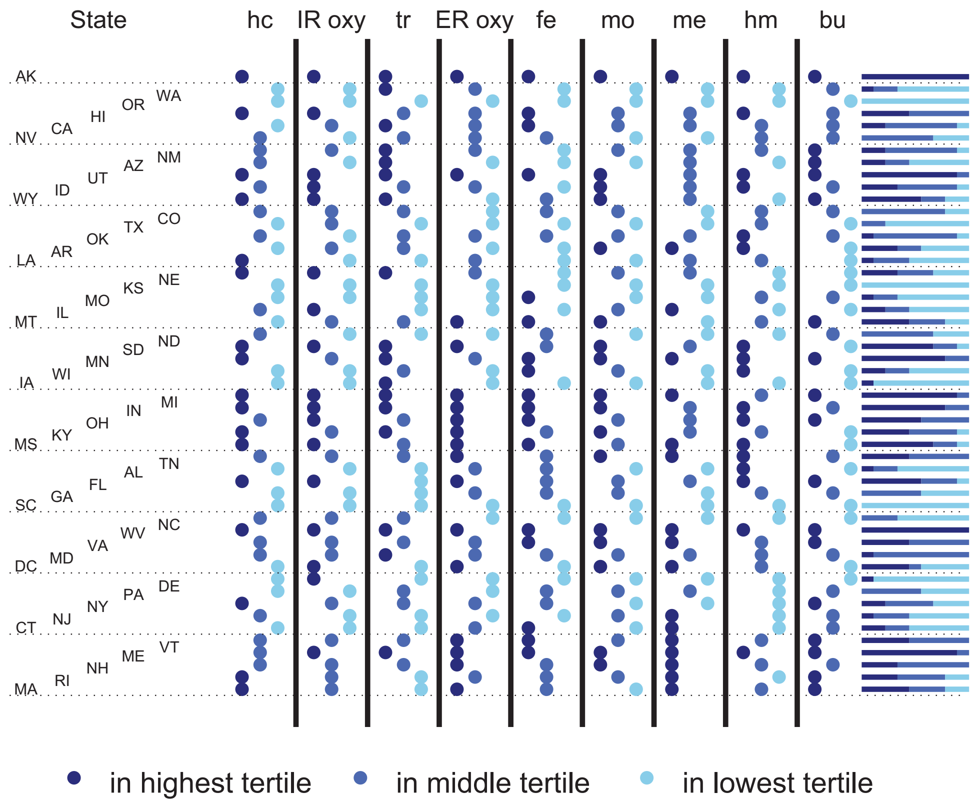

Figure 3. Linearized map of the tertiles of statewide rates of prescription opioid abuse: combining four signal detection systems (OTP, Key Informants, Diversion, Poison Centers) for each prescription opioid; hc = hydrocodone, IR oxy = Immediate Release oxycodone, tr = tramadol, ER oxy = Extended Release oxycodone, fe = fentanyl, mo = morphine, me = methadone, hm = hydromorphone, bu = buprenorphine

Figure 4) to produce an overall percentile of prescription opioid abuse for each state, incorporating the 36 nationwide rates of abuse from the nine drugs and according to the four systems. We developed our methodology to integrate both signal detection systems that collect data from heterogeneous populations and drugs with heterogeneous abuse rates to summarize abuse at the statewide level. While other monitoring systems such as DAWN collect data from many different drugs, the data sources are Emergency Departments, which provide data on drug-related hospital emergency department visits as opposed to four very different systems that we have integrated to provide a more robust measurement of abuse.

By incorporating the nationwide rates of abuse into the calculation of a state's abuse percentile, we allow drugs with heterogeneous nationwide rates to contribute differently to the summary metric. For example, within any signal detection system, a state with the highest rate of methadone abuse was treated differently than a state with the highest rate of tramadol abuse, since tramadol had a much lower nationwide rate of abuse in each of the four systems (see Table 3). In contrast, using the average or median ranking of abuse of all nine drugs when determining the overall statewide percentile would inappropriately equate the abuse rate of all nine drugs (i.e., treat the state with highest ranking of tramadol the same as the state with the highest ranking of methadone abuse). The same is true when calculating a statewide percentile for a given drug integrating across all four signal detection systems; if the four rankings were simply averaged, then all four signal detection systems would be treated equally (i.e., weights = ¼) even though they have different nationwide abuse rates (Table 3). To compare our proposed weighted approach to the unweighted approach of simply averaging the four rankings from different signal detection systems, we determined the correlation of the states scores for each of the nine drugs using both approaches. Except for tramadol (correlation = 0.88), the correlation coefficients for the other eight drugs were >0.95. This is consistent with the weights for tramadol in Table 3 (10.9, 13.1, 9.7, and 66.4%) being the farthest from (25, 25, 25, and 25%) compared to the weights of the other eight drugs. Hence, for a given drug, if our proposed weights are

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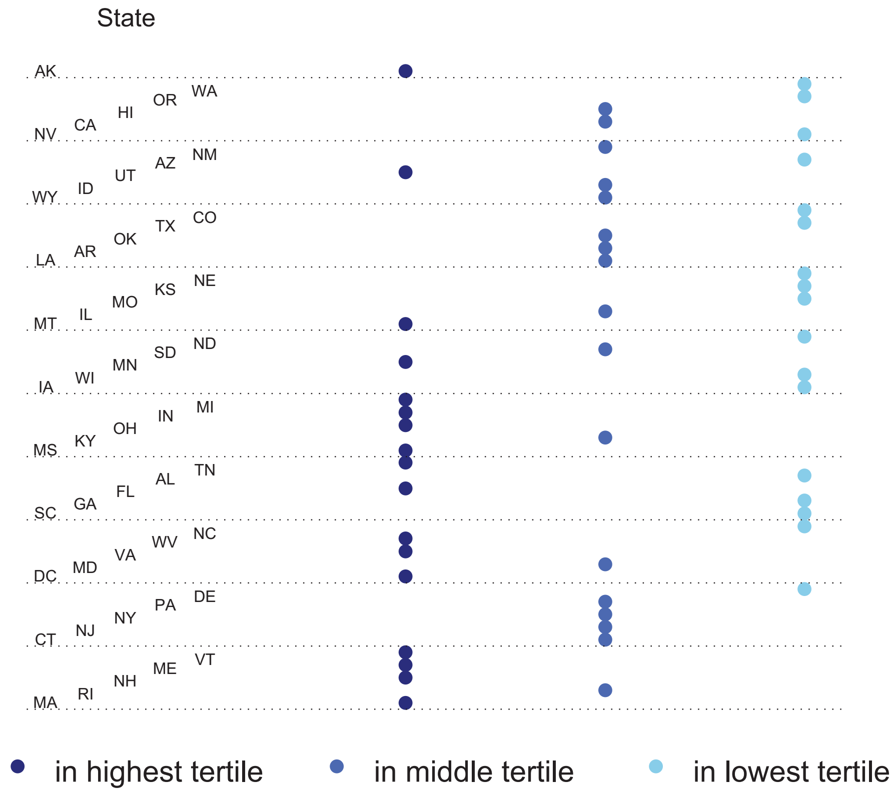

Figure 4. Linearized map of the tertiles of statewide rates of prescription opioid abuse: combining nine prescription opioids (hydrocodone, IR oxycodone, tramadol, ER oxycodone, fentanyl, morphine, methadone, hydromorphone, buprenorphine) and four signal detection systems (OTP, Key Informants, Diversion, Poison Centers)

similar in value (i.e., all close to 25%), then the statewide rankings of abuse will be very similar, regardless of approach. Otherwise, our proposed weights may offer a better description of the combined ranking of abuse in different states. Needless to say, if a state has the highest ranking of abuse in each signal detection system for a given drug, the weighting approach would be irrelevant as the value of the state score would always equal 1. Although the weighting methods we provided here attempt to incorporate heterogeneity among the sources being integrated, full characterization of the settings for when the proposed methods will be optimal will require simulation studies beyond the scope of this work.

Our methods integrate the ranking of statewide abuse rates instead of the values of the rates themselves. Non-parametric methods that utilize ranks instead of the actual rates limit the influence of unduly large or small statewide rates (i.e., outliers) on any conclusions made, and also do not require any distributional assumptions for the statewide rates (e.g., Poisson distribution). We have chosen to concentrate on applying methods to appropriately describe statewide prescription drug abuse. Further development of our methods are needed to quantify standard errors, which will allow for significance testing and would include a formal test of heterogeneity of the nationwide rates of abuse of different drugs and/or signal detection systems.

While we have calibrated our statewide percentiles for drugs and/or signal detection systems with different overall nationwide rates, we have kept time constant (i.e., analyses for 2007 only). Our methods could be extended to describe the temporal changes of statewide abuse of a given drug. Specifically, for a given drug, once the information of the signal detection systems is combined for each year, linearized maps for a series of years could be presented in one graph to determine where a state's abuse ranks over time while also depicting the persistence of abuse in a given state over time. In our final linearized maps we have chosen to group the statewide percentiles into three tertiles; this was arbitrary since quartiles, quintiles, deciles, or any quantiles could be used as cut points to summarize the statewide percentiles. Furthermore, the methods presented here summarize the ranking of abuse at the state level; thus, our methods have limited applicability when the aim is to identify more precise locations (i.e., 3DZ) with excessive rates of abuse. Alternative

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methods would be more appropriate when locating more geo-specific ''signals'' of abuse is the goal of interest.[19] Additionally, since both Drug Diversion and Poison Centers have greater 3DZ coverage within states than both OTP and Key Informants (Table 1), from a strictly 3DZ coverage perspective, the statewide rankings of abuse used in our non-parametric analyses using Drug Diversion (39% of states with complete 3DZ coverage) and Poison Centers (35 of 40 [88%] states with at least some 3DZ coverage have complete coverage) could be considered more reliable than OTP (1 of 35 [3%] states with at least some 3DZ coverage have complete coverage) and Key Informants (1 of 46 [2%] states with at least some 3DZ coverage have complete coverage). However, Table 1 also illustrates that with the exception of Drug Diversion, there is similar coverage across states within a given signal detection system. Thus, statewide rates and their rankings are based on a similar percentage of coverage.

We have shown that many of the highest rates of prescription opioid abuse have taken place in northeastern states (Massachusetts, New Hampshire, Maine, Vermont) and also Appalachian states (Virginia, West Virginia, Tennessee, Mississippi, and Ohio). These results are in accordance with others who have also reported high rates of abuse in northeastern parts of the United States and Appalachia.[20–22] Specifically, when both drugs and signal detection systems were integrated, only four states west of Michigan (Minnesota, Montana, Utah, and Alaska) have percentiles in the highest tertile (as shown in Figure 4). When the nine drugs were integrated across each signal detection system (Figure 2), the states classified as having high rates of abuse were very similar to those identified in Figure 4 with the exception of Key Informants, who had a similar spread of states in each tertile. In addition, there was good agreement between states in the highest tertile in Figure 4 and the states with longest dark lines in the bar graph in Figure 3; likewise, the states in the lowest tertile are frequently those with the longest light-colored lines. Such consistencies confer internal validity to our proposed methods.

KEY POINTS

- We present non-parametric methods to integrate statewide rankings of abuse across nine prescription opioid analgesics (hydrocodone, immediate-release oxycodone, tramadol, extended-release oxycodone, fentanyl, morphine, methadone, hydromorphone, and buprenorphine) and/or four signal detection systems (Opioid Treatment Programs, Key Informants, Drug Diversion, and Poison Centers) to summarize statewide prescription drug abuse in the United States in 2007.
- When statewide rankings of abuse were integrated across nine drugs for each signal detection system, Rhode Island, New Hampshire, Maine, West Virginia, and Michigan were in the highest tertile of abuse in three of four signal detection systems.
- When statewide rankings of abuse were integrated across four signal detection systems for each drug, there was a geographic clustering of states with the highest rates for ER oxycodone (in Tennessee, Mississippi, Kentucky, Ohio, Indiana, Michigan, and in Massachusetts, New Hampshire, Maine, Vermont) and for methadone (Massachusetts, Rhode Island, New Hampshire, Maine, Vermont, Connecticut, New Jersey).
- When statewide rankings of abuse were integrated across both drugs and signal detection systems, states with 3-digit ZIP codes below 269: Massachusetts, New Hampshire, Maine, Vermont, Washington DC, Virginia, and West Virginia were in the highest tertile and only Delaware was in the lowest tertile.
- By capitalizing on the numerical order of the three-digit ZIP codes by states, we provide ''linearized maps'' a novel graphical procedure to simultaneously and succinctly depict several maps in one figure to facilitate the comparison of signal detection systems and/or drugs of interest.

CONCLUSIONS

We have presented methods to integrate data on rates of prescription opioid abuse collected by signal detection systems covering different populations. Although we have integrated signal detection systems that cover heterogeneous populations to illustrate differences in the level of abuse at the state level, as with any sampling scheme, our conclusions are subject to how representative the aggregate sample comprised of four different signal detection systems is of the population of interest. The design of intervention strategies to reduce and control abuse of prescription drugs needs actions at the state level, but also typically requires the description at more localized levels (e.g., 3DZ) and complementary studies to characterize the nature of abuse. The full epidemiological description of the nature of abuse of prescription drugs is a key component of maintaining the benefit of effective drugs while controlling their potential abuse.

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APPENDIX

The nationwide rates of abuse per 10 000 URDD ($r^{sds,d}$) were determined for each signal detection system (*sds*: 1 = OTP, 2 = Key Informants, 3 = Drug Diversion, 4 = Poison Centers) and for each drug (*d*: 1 = hydrocodone, 2 = IR oxycodone, 3 = tramadol, 4 = ER oxycodone, 5 = fentanyl, 6 = morphine, 7 = methadone, 8 = hydromorphone, 9 = buprenorphine) and used to appropriately integrate all nine drugs for a given signal detection system and/or integrate all four signal detection systems for a given drug.

Integrating rankings of statewide abuse across drugs within each signal detection system

For each of the four signal detection systems in 2007, we calculated rates of abuse of drug *d* assessed by signal detection system *sds* in state *s* by dividing the total cases reported at the covered 3DZ in *s* by the total URDD at the covered 3DZ in *s*. For each signal detection system *sds* and each drug *d*, we denote the rank of the statewide rate by $R_s^{sds,d}$ (e.g., if $R_s^{sds,d} = 7$ then state *s* has the 7th lowest rate for drug *d* among the states covered by the signal detection system *sds*) and we denote the number of states covered by a given signal detection system *sds* by N^{sds}. In order to standardize the rankings to a range of 0 to 1 for signal detection systems with different N^{sds}, we divided each ranking $R_s^{sds,d}$ by N^{sds} such that the state with the lowest rate for drug *d* for signal detection system *sds* was assigned a ranking of ($1/N^{sds}$), and the rankings for subsequent statewide rates increased by the same amount of ($1/N^{sds}$). For example, in OTP ($sds = 1$), the state with the lowest rate of abuse for drug *d* was assigned a standardized ranking of 1/35 since $N^1 = 35$, the state with the second lowest rate of abuse was assigned a ranking of 2/35, the state with the second highest rate of abuse was assigned a ranking of 34/35, and the state with the highest rate of abuse was assigned a ranking of 1 (=35/35).

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Once a standardized rank $R_s^{sds,d}/N^{sds}$ for state s is determined for signal detection system *sds* and drug d, we calculated an overall rank of abuse across the nine drugs according to the nationwide rates for the drugs in the signal detection system *sds* ($r^{sds,d}$). Specifically, when integrating all nine drugs, the weights $v^{sds,d} = r^{sds,d} / \sum_{j=1}^{9} r^{sds,j}$ were used to appropriately account for the heterogeneity in the nationwide rates of abuse of different drugs within each signal detection system. In order to combine the rankings of the nine drugs within a given signal detection system *sds*, the standardized ranking $R_s^{sds,d}/N^{sds}$ of state s was multiplied by the nationwide weight for drug d, and it was these products that were then summed over all nine drugs to obtain a statewide score $R_s^{sds,\bullet} = \sum_{j=1}^{9} \left[\left(R_s^{sds,j}/N^{sds} \right) v^{sds,j} \right]$. Since $\sum_{j=1}^{9} v^{sds,j} = 1$ for each *sds*, it follows that the scores $R_s^{sds,\bullet}$ for the states in a given *sds* represent percentiles of the abuse of opioids within a given *sds*.

Integrating rankings of statewide abuse across signal detection systems for each drug

To integrate signal detection systems for a given drug, we needed to calibrate for the differences between the four signal detection systems, as signal detection systems have access to different populations. To incorporate the overall rate in populations monitored by different *sds*, we used the median nationwide rate of abuse for each signal detection system denoted by m^{sds} (i.e., m^{sds} = median of $r^{sds,1}, r^{sds,2}, r^{sds,3}, r^{sds,4}, r^{sds,5}, r^{sds,6}, r^{sds,7}, r^{sds,8}, r^{sds,9}$). Specifically, to calibrate the nationwide rates for drug d within each signal detection system *sds*, we first divided $r^{sds,d}$ by m^{sds}. This ratio represents how large the nationwide rate of abuse for drug d was relative to the median nationwide rate of abuse of the nine drugs within a given signal detection system. Dividing by the median rate attenuates the effect that one large rate from any one signal detection system would have, when integrating nationwide rates across all systems. When integrating across signal detection systems for a given drug d, the weights $w^{sds,d} = \left(r^{sds,d}/m^{sds} \right) / \sum_{i=1}^{C} \left[r^{i,d}/m^{sds} \right]$ where C = the number of signal detection systems covering each state were used to adjust for the heterogeneity in the nationwide rates of abuse between the signal detection systems for a given drug.

In order to combine the rankings of the signal detection systems for a given drug d, the ranking of state s divided by N^{sds} was multiplied by the nationwide weight for signal detection system *sds* and it was these products that were then summed over all signal detection systems to obtain statewide score $R_s^{\bullet,d} = \sum_{i=1}^{C} \left[\left(R_s^{i,d}/N^{i} \right) w^{i,d} \right]$. Since $\sum_{i=1}^{C} w^{i,d} = 1$ for each drug d, it follows that the scores $R_s^{\bullet,d}$ for the states for a given drug d represent percentiles of the abuse of opioids for that specific drug.

Integrating rankings of statewide abuse across drugs and signal detection systems for one nationwide map

In order to combine the rankings of both drugs and signal detection systems, the rankings of state s were multiplied by the weights $x^{sds,d} = \left(r^{sds,d}/m^{sds} \right) / \sum_{i=1}^{C} \sum_{j=1}^{9} \left(r^{i,j}/m^{i} \right)$ and it was these products that were then summed over all signal detection systems and all nine drugs to obtain an overall statewide score $R_s^{\bullet,\bullet} = \sum_{i=1}^{C} \sum_{j=1}^{9} \left[\left(R_s^{i,j}/N^{i} \right) x^{i,j} \right]$. Since $\sum_{i=1}^{C} \sum_{j=1}^{9} x^{i,j} = 1$ it follows that the scores $R_s^{\bullet,\bullet}$ for the states represent percentiles of the distribution of rates of opioid abuse.

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